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TITLE: A Randomized, Placebo-Controlled Trial of D-Cycloserine for the Enhancement of Social Skills Training in Pervasive Developmental Disorders

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ABSTRACT

The main objective of this application is to determine whether D-cycloserine (DCS) can enhance the efficacy of social skills training (SST) in the treatment of children and young adolescents with autism spectrum disorders (ASDs). We will evaluate the efficacy, tolerability, and last effects of DCS given one hour prior to each of 10 weekly SST sessions for the treatment of social impairment in 52 children and young adolescents (ages 5-11 years) with ASDs during a randomized placebo-controlled trial. The safety and tolerability of DCS and durability of treatment response will also be examined. Institutional IRB and Department of Defense Human Research protections Office approvals have been obtained. Staff have been hired and trained on study procedures. The first ten groups of 6 youth (per group: 4 with ASD and 2 normally developing children) have completed the first SST group and the eleventh and twelfth groups are active in the trial due to complete 10 weeks of treatment in March 2012. We have a set schedule for 4 groups per year. In 2011 received IRB approval of an amendment to allow for enrollment of youth with stable seizure disorders and youth who take up to two concomitant psychotropic non-glutamatergic drugs. In addition we have received IRB approval to add use of the Autism Diagnostic Observation Schedule to better characterize ASD pathology. In 2012 the study was expanded to potentially include a second site, led by former Indiana University site PI Craig Erickson, at Cincinnati Children's Hospital Medical Center. Dr. Noha Minshawi was named lead PI at the Indiana University Site at that time.

INTRODUCTION

The long-range goal of this research is to identify better treatments for the core social and communication impairment of autism spectrum disorders (ASDs). The main objective of this application is to determine whether D-cycloserine (DCS) can enhance the efficacy of social skills training (SST) in the treatment of children and young adolescents with ASDs. The central hypothesis is that DCS will enhance the learning of social skills over the course of 10 weeks of SST. To test this hypothesis, we will evaluate the efficacy of DCS given one hour prior to each of 10 weekly SST sessions for the treatment of social impairment in 52 children and young adolescents (ages 5-11 years) with ASDs during a randomized placebo-controlled trial. The safety and tolerability of DCS and durability of treatment response will also be examined.

BODY

Final IRB approval was obtained August 5, 2009. Initial revisions requested by the Department of Defense Human Research Protections Office (HRPO) were received and processed in an IRB amendment approved on December 25, 2009. Final revisions then requested by the HRPO were submitted to our IRB and final approval was received February 4, 2010. During the initial funding year staff were hired and trained to conduct this study. Source documents were created. Staff was trained on the execution of the protocol and on the outcome measures employed in the protocol. Procedures for dispensing and tracking drug were established with Investigational Drug Services. Arrangements for obtaining drug and matching placebo were made. The SST curriculum, including lesson plans, homework assignments, and parent notes was finalized during the first study year. Supplies for the SST were purchased. Visual supports for the curriculum were created. A procedure for coding and ensuring treatment and rating fidelity was established. Due to the amount of preparation required and difficulties with recruitment early on, the study only enrolled 4 children with ASD and 2 typically developing peers in the first year of funding. From March 1, 2010 to February 28, 2011 we completed 4 social skills training groups

each enrolling 4 youth with ASD and 2 youth with neurotypical development who served in each group as peer trainers. In 2011 we enrolled and completed study with 16 youth with ASD and 8 youth with neurotypical development. In 2012 we enrolled and completed study with an additional 16 youth with ASD and 8 youth with neurotypical development.

During 2012 we made the decision to ask the Department of Defense if we could be allowed to expand the project to a two site study. Dr. Craig Erickson the Site PI at the Indiana University sub-recipient site decided to leave Indiana University and move his research program to Cincinnati Children's Hospital Medical Center. We felt that Dr. Erickson's move presented an opportunity to boost overall subject recruitment into this project to increase the power of the study. After discussions with representatives of the Department of Defense, we are now in the process of seeking approval for a second Cincinnati recruitment site where Dr. Erickson would, if allowed, enroll an additional 4 subjects with ASD in 2012 and 12 additional subjects with ASD in 2013. Under this plan, which has not yet received final Department of Defense contracting and human subject's protection office approval, the overall study N would increase to 68 youth with ASD and 34 neurotypical peers. This change is being proposed without adding any additional expense to the project. With Dr. Erickson's move, we have also applied for and received approval to appoint Dr. Noha Minshawi the Site PI at the Indiana University sub-recipient site effective 6/18/12.

From July to October 2012, the Cincinnati site worked to obtain local and Department of Defense regulatory clearance to begin study procedures. Since beginning study enrollment in the late Fall of 2012, the Cincinnati site has completed one social skills group (4 youth with ASD and 2 peer youth with neurotypical development) and the Cincinnati site has one social skills group currently ongoing. The Cincinnati site will enroll another 8 youth with ASD and an additional 4 peers with neurotypical development for two summer 2013 social skills training groups beginning in late May 2013. The total Cincinnati enrollment continues to project to be 16 subjects with ASD and 8 neurotypical peers.

KEY RESEARCH ACCOMPLISHMENTS

- From March 1, 2012 to December 31, 2012 we completed 4 social skills training groups each enrolling 4 youth with ASDs and 2 youth with neurotypical development who served in each group as peer trainers. Given this, we enrolled and completed study with 16 youth with ASDs and 8 youth with neurotypical development during this time period. All groups met recruitment goals on time and we achieved our overall goal to complete 4 groups during the 2012 calendar year. We have set a schedule to conduct four subject groups per 12 months until enrollment is completed.
- In the fall of 2011 we additionally added a novel pilot analysis of eye tracking to the protocol. This paradigm utilizes a hands-free tabletop Tobii T120 eye tracking unit to assess the eye gaze of subjects with ASD pre- and post-social skills intervention. Use of this non-invasive additional quantitative means to assess eye gaze in social setting holds promise to serve as a potential outcome measure for future related projects. This tracking equipment was provided by the sub-recipient Indiana University site at no cost to the project.
- In 2012, research posters were presented at two professional conferences: International Meeting on Autism Research (IMFAR; Toronto, Canada) and the Association of

Behavioral and Cognitive Therapies (ABCT; Washington, D.C.). These posters focused on the development of the social skills curriculum and behavioral data collection models in use for this study. Both posters were very well received.

REPORTABLE OUTCOMES
We expect most of the reportable outcomes of this award will be realized in the later years of the project.

CONCLUSION
Since this is a clinical trial, the results will be analyzed after all subject data collection has been completed (Year 5).

REFERENCES:
None.

APPENDICES:
None.

SUPPORTING DATA:
None.